Remarks

Claims 1-2, 7-9, 12-22 and 27-60 have been canceled and Claims 61-65 have been added. The claims now present in this application are Claims 4-6, 10, 11, 23-26 and 61-65.

In view of the cancellation of claims 16-22 and 49-54, the Restriction Requirement is no longer an issue. In addition, in view of the cancellation of Claims 30-48 and 55-60, the failure of the claims to receive the priority date of the provisional is no longer an issue.

At the outset, Applicant's attorney wishes to thank the Examiner in charge of the application and the primary Examiner for the courtesies extended to him during the course of the interview on May 9, 2002. During this interview, Applicant's attorney discussed the outstanding rejection and the prior art references and in particular pointed out that this invention was directed to a conjugate which consisted of three parts, i.e., the EPO, the PEG moiety and the linking group. It is the specifics with regard to each of these elements or parts which form the claimed invention.

Accompanying this Amendment is an Information Disclosure Statement setting forth various prior art references and in particular, the Katre and Nishimura Patents. The Katre and Nishimura Patents demonstrate that the members in a tripart conjugate of a protein linker and PEG moiety are not interchangeable. In particular, these patents demonstrate, as pointed out at the aforementioned interview, that various linking groups are not equivalent in producing PEG/protein conjugates. In this regard, these U.S. Patents demonstrate that the use of linking agents in forming a therapeutic useful conjugate is not often predictable and varies depending upon the protein and the specific linking agent used.

In accordance with the aforementioned interview, Applicants are submitting a Declaration by the inventor, Pascal Bailon, which further emphasis the conclusions in the Katre and Natecki Patents. As seen from the results reported in this Declaration, the biological activity of EPO conjugates to enhance the growth of red blood cells for long periods of time after administration depends upon the type of linking agents used. This

type of conjugation includes the linkage and linker between the EPO and the PEG moiety. Furthermore, these results demonstrate that even a three carbon methylene bridge separation between the amide bond and the PEG moiety produces far greater beneficial results than the corresponding conjugate with only a two carbon methylene bridge separation.

The results in this Declaration demonstrate that even the conjugate of this invention, with a two carbon separation, provides new and unexpected results over the conjugates with other types of linkages. Please note that the only exception is the conjugate disclosed in Berg et al., U.S. Patent 6,340,742. However, this Berg et al. patent is not a reference against this application. Please note that the captioned application has an effective filing date of July 2, 1999 based upon provisional application 60/142,254 as noted on page 2 of the aforementioned Office Action. On the other hand, the earliest filing date that Berg can claim is July 2, 1999 based upon provisional application 60/142,243. Since the Berg Patent has the same effective filing date as the captioned application, the Berg et al. Patent cannot be utilized as a reference against the instant application. Claims 30-48 and 55-62 have been canceled from this application. Therefor there is no issue as to whether the instant claims are entitled to the July 2, 1999 filing date of the provisional application 60/142,254

Even if the Berg patent were a reference, which certainly is not the case, it would not render obvious the claimed conjugates. Comparing the structures of Berg conjugate, Compound V, with the structures of conjugates of this invention, Compounds I and II, it is clear that the structure of the conjugates of the Berg patent in no way resembles the claimed structure. Nothing in the Berg reference suggests forming the conjugates with the claimed amide linkage and linkers. Berg does not disclose the claimed amide linkage . Besides this, the linkers that Berg does discloses in column 2, lines 15-30, are structurally remote from the claimed linking groups of this invention. Clearly there is no structural similarity between the conjugates of this invention and the conjugates of Berg. However the results reported with respect to these conjugates in the Bailon Declaration ,including the conjugates of Berg, reinforce

that activity of a conjugate even with a given protein depends upon the type of conjugation which includes the linkage and linker between the protein and the PEG moiety .

In accordance with this amendment, the claims have been simplified and amended to recite that they cover conjugates having mono amide linkage between the protein and the PEG moiety with a specific linker separating the amide bond from the PEG moiety. In accordance with this invention, the EPO and PEG conjugates are amide conjugates linked via two to three carbon atoms separation between the amide bond and the PEG moiety. In addition, new claims 63-65 have been presented specifically limiting the linkage between the amide bond and the PEG moiety to a three carbon atom linkage.

As pointed out in the aforementioned interview, Applicants are enclosing as part of the Information Disclosure Statement, the European Application of Campfield et al., EP 741 187 published on November 11, 1996,0 This EP publication should be substituted for the Bailon et al U.S. Patent 6,025,324. cited in the aforementioned Office Action. Please note the Disclosure Statement with the PTO-1449 Form setting forth this Campfield European Patent. The Campfield et al. EP, contains the pertinent disclosure present in the Bailon et al. U.S. Patent. Since the Campfield et al. EP contains this disclosure, it constitutes a publication of the Bailon et al. patent more than one year prior to the filing date of the captioned application. Therefore, unlike the Bailon patent, it cannot be removed as a reference in accordance with the suggestions made on pages 4-5 of the outstanding Office Action. In addition, the issue of obvious double patenting over the claims of this Bailon et al US patent is converted into an issue of obviousness. Unlike the Bailon et al. US patent, the Campfield EP cannot be removed as a reference by means of a Terminal Disclaimer.

Claim 4 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite with regard to the use of the term "endogenous activation" which describes the particular method by which the EPO in the conjugate is prepared. Please note that

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"endogenous activation" does not describe the conjugate but merely the EPO within the conjugate.

A rejection under 35 U.S.C. §112, second paragraph, must be based upon the fact that one skilled in the art could not ascertain what is meant by the term "utilized in the claim." Please note In re Robins, 166 USPQ 552 at 556, where the CAFC held that such terms such as "aryl," and "substituted aryl radicals" are not indefinite under 35 U.S.C. §112, second paragraph, since one skilled in the art could ascertain what is encompassed within the meaning of this term. In the same way "endogenous activation" defines a well known method of protein preparation especially EPO which method could be easily ascertained by one skilled in the art. In this regard, please note page 6, lines 15-20, of the instant application, which specifically sets forth the various U.S. and foreign patents which teach expression of proteins, including EPO by endogenous gene activation.

As pointed out in the aforementioned interview, the district court in their decision in Amgen v. Hoechst, 57 USPQ 2d. 1449, utilized the term "endogenous gene activation" on pages 1465, 1471 and 1473 of this decision. It was TKT's (Hoechst) use of an endogenous gene to make EPO by ligating a promoter or activator in the human EPO producing cell that formed the basis for the District Court of Massachusetts holding of non-infringement in this case . Please note the statement of the district court in 57 USPQ 2d 1449 at 1473, as follows:

> "Thus, because of TKT's use of both endogenous rather than exogenous DNA and a viral promoter located far upstream from the EPO coding region, as well as other less fundamental distinctions, TKT is entitled to judgment of non-infringement on the '698 patent both literally and under the doctrine of equivalents."

Based on the foregoing, it can be seem that "endogenous gene activation" is a term well known in the prior art. Clearly the use of this term to define the EPO in a claimed EPO conjugate does not render the claim indefinite.

The claims have been rejected under 35 U.S.C. §103(a) as obvious over Kawaguchi et al. in view of Bailon, Hakimi and Elliott. As described hereinbefore the Campfield reference cited in the Information Disclosure Statement should be substituted for the Bailon et al. patent. This rejection is respectfully traversed

Contrary to the assertion in the aforementioned Office Action, none of the references used in this rejection, i.e., Kawaguchi et al. or Elliott, show a conjugate of EPO with polyethylene glycol. In Kawaguchi et al. polyethylene glycol is not used as part of a conjugate but is a separate ingredient used as a stabilizer in a composition with EPO. Elliot discloses EPO itself and not as a conjugate much less a conjugate with PEG. The PEG in Kawaguchi et al is an ingredient in a formulation with EPO and it does not form a conjugate which can be administered as a unitary pharmaceutical. In place of PEG stabilizers, Kawaguchi et al. disclose that various conventional stabilizers can be utilized including bovine serum albumin, and gelatin. Applicants are not stabilizing a preparation of EPO prior to its administration. Applicants are providing a conjugate which upon administration retains the immunological properties of the EPO . However due to its conjugation with PEG, the conjugate when compared to the EPO protein itself has a longer half life and remains active in the system for long periods of time. These improved therapeutic properties as compared to EPO itself can be seen from the Bailon Declaration. There is nothing in the Kawaguchi et al. or Elliott reference which would disclose conjugating EPO with a PEG moiety.

On the other hand, attention is directed to the Wright et al. patent set forth Information Disclosure Statement. This patent discloses the use of EPO conjugated to a PEG via a hydrazine derivative. The conjugation with a hydrazine derivative is different than the claimed EPO PEG amide conjugate of this invention In the hydrazine derivative conjugate, there is no amide linkage. In fact, as seen from Bailon's Declaration, the hydrazine is linked by a sugar moiety not an amine moiety to the EPO. In addition there is a diazide linkage and no separation of 2 to 3 carbon atoms between the amide linkage and the PEG moiety.

Hakimi et al. disclose various linkages between a protein and the PEG moiety. However, none of these linkages are amide linkages. These linkages are either urea or urethane type linkages with functional groups on both sides of a carbonyl or thio - carbonyl group. In fact, even between these functional groups there is no 2 or 3 carbon methylene bridge such as in the claimed conjugates of this invention. The only type of linking group related to that claimed is found in the Campfield reference. Here there is an amide linkage which is separated by 2 carbon methylene chain . Please note Formula IB on page 10 of this reference. However, the protein that is utilized in the Campfield reference is the OB protein. Nothing in Campfield or for that matter any other reference would suggest substituting the EPO for the OB protein in the Campfield conjugate . Furthermore, even if such a substitution were to be made, there would only be a 2 carbon methylene bridge rather than a 3 carbon methylene bridge between the PEG moiety and the amide group. In addition, there is nothing that would suggest that by such substitution one could achieve the unexpected results for the claimed EPO conjugates demonstrated in the Bailon Declaration especially with regard to results obtained for the amide conjugates separated from the PEG moiety by a 3 carbon methylene bridge.

As pointed out in the aforementioned interview, all of the claims are directed to a tripart conjugate of a water soluble polyethylene glycol (PEG) and EPO linked by an amide group through a carbon chain of from 2 to 3 atoms. None of the references teach, much less suggest, the claimed tripart conjugate.

The Katre and Nishimura patents set forth in the Information Disclosure Statement demonstrate that that the members in this tripart conjugate are not interchangeable . The Katre and Nishimura patents demonstrate that various linking agents are not equivalent in forming conjugates. In this regard these patents demonstrate that their use in forming a therapeutic useful conjugate is not predictable and varies depending upon the protein and the specific linking agent used. The question of whether a linking agent with a given protein and a given PEG moiety will produce a therapeutically useful reagent depends upon the given linker and the protein

in which its used Therefore these patents demonstrate that the success of one linking group with a given protein to form a PEG conjugate does not mean that it could be utilized with other proteins much less the specific protein EPO.

Nishimura teaches against using certain types of linkers, disclosing that undesirable properties occur with conjugates that have certain type linkers between the protein and the PEG molecule. For example the coupling agents used to make linked conjugates can damage the proteins (page 2, lines 20-24, page 3, lines 15-17, 20-23 of Nishimura). It is for this reason that Nishimura decided to dispense with linkers and make a conjugate where the PEG is directly linked to the protein.

Katre also demonstrates that enhancement of the biological activity of proteins for therapeutic administration by conjugation with polyethylene glycol is basically a selective process and depends upon the specific protein and linking agent. As stated in column 3, lines 54-59 of the Katre '888 patent:

> Furthermore, it is not *a priori* possible to predict which selected proteins would be favorably responsive to treatment with polymers due to the vast difference in pharmacokinetics and physical properties of various proteins.

Katre clearly demonstrates that one cannot predict whether beneficial or deleterious properties would be imparted to the biologically active protein through its conjugation to PEG. Katre teaches that favorable properties depend upon the specifics as to the PEG, linker and the protein. Clearly, this is not a teaching of the equivalence of all proteins, PEG, polymers and linkers for this purpose. That materials may be classified as biologically active proteins, water soluble PEG polymers or linkers does not make them equivalent.

Katre specifically states that the process of his invention is limited to a specific linker with three Nishimura specific proteins, such as IL-2 and interferon-β. As stated in column 8, lines 49-61of the Katre patent :

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> "According to the process of this invention, the three types of proteins described above which are normally hydrophobic and water insoluble, are rendered soluble in an aqueous carrier medium ... by modifying the protein through conjugation to a specified polymer ... The success of such modifications of these proteins cannot be predicted from early use of polymer modification of water soluble enzymes and hormones." (Emphasis Added)

Certainly, this is not a teaching that the individual elements or parts of the conjugates utilized in Katre are applicable to all hydrophobic, water insoluble polymers but rather only to the three specific types of proteins with the specific types of linking.

That the use of specific linkers and that the properties produced with a given protein vary in accordance with a specific linker is also demonstrated by the results in the Bailon Declaration This can be seen from the results obtained by merely adding a single methylene bridge between the amino group and the PEG moiety which produces superior results with regard to the ability of the conjugate to assert its biological effects over a far longer period of time. In addition, this Declaration shows that with certain linking groups, different biological results are achieved.

None of the cited references disclose the possibility of substituting the PEG linker utilized in Campfield for the linking system in Wright to produce an EPO PEG amide conjugate, much less the EPO amide conjugate linked via 3 carbon methylene bridges. In fact, none of the references set forth the possibility that the amide linkage of Campfield could be utilized successfully with EPO to produce an EPO conjugate. The OB protein is a totally different protein from EPO, different in properties and structure from EPO. No basis exists or is set forth for holding these proteins equivalent.

To combine references on the basis that one could substitute a material of one reference for different material disclosed in another reference as a design choice is not sufficient for obviousness rejection without a suggestion in the art to make this substitution and that success would result. No such suggestion appears in any of these references. Attention is directed to In re Vaeck, 20 USPQ 2d 1442 (Fed. Cir. 1991) where the claimed invention was directed to a chimeric gene capable of being expressed in

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cyanobacteria composed of the DNA for such expression and the gene fragment encoding an insecticidal active protein. The CAFC held that a rejection could not be based upon combining a reference disclosing a chimeric gene for cyanobacteria expression which included this cyanobacteria expression DNA fused to another structural encoding gene combined with another reference disclosing the claimed gene fragment encoding the insecticidally active protein. In so holding, the CAFC stated

> Where the claimed subject matter has been rejected as obvious in view of a combination under §103 requires, *inter alia*, consideration of two factors : (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success... Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. (Emphasis Added)

As seen from this decision, for an obviousness combination rejection, the references must do more than provide a design choice to make obvious the modifications which produce the claimed product. The references must provide both basis for combining these references to obtain the conjugate and for the reasonable expectation that success would be achieved by this combination. No basis exists in the references for making the required substitution. In addition the references do not disclose that by making such substitution, one would achieve a successful result. In fact, as pointed out hereinabove, the prior art teach against such substitution and it would not be obvious to select a specific linker for linking a given protein such as in this case, EPO to PEG. Unobviousness is emphasized by the fact that as seen from the Bailon Declaration, new and unexpected results are achieved when this specific linker is used with EPO to form a PEG conjugate.

It cannot be seen how the Berg et al. patent adds anything to the rejection. In fact, as pointed out above, the Berg Patent does not constitute a reference which can be cited against the instant claims. However, that said, it still provides a totally different conjugate and structure from that claimed in this application. Clearly the Berg et al.

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patent taken as a reference or removed in accordance with applicable U.S. law cannot constitute a basis for rejecting the claims of this invention.

With regard to the double patenting over the claims of Bailon et al. as pointed out before, Bailon taken together with all of the other references, before and after even applying its full disclosure still does not render obvious the claimed invention. Bailon utilizes the linking group with the two carbon separation and with OB protein. There is nothing in the prior art which suggests, much less renders obvious, the use of this linking group with EPO. No basis is set forth as to why the use of a certain linking group with OB protein would render obvious the use of this linking group with EPO.

Based upon the foregoing, it is submitted that all of the claims in this application are in condition for allowance. A prompt Notice of Allowance is respectfully requested.

Correspondence and Fees

Enclosed please find a check in the amount of One Hundred and Eighty Dollars ($180.00) to cover the Information Disclosure Statement being filed herewith. No additional fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 03-3839 for any underpayment, or to credit any overpayments.

Please address all correspondence to Intellectual Property Docket Administrator, Gibbons, Del Deo, Dolan, Griffinger & Vecchione, One Riverfront Plaza, Newark, NJ 07102-5497. Telephone calls should be made to William H. Epstein at (973) 596-4607 or (973) 596-4500 and fax communications should be sent directly to him at (973) 639-6394 or (973) 596-0545.

Respectfully submitted.

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Version With Markings to Show Changes Made

3. (Amended) The conjugate of claim [2] 62, wherein the glycoprotein is human erythropoietin.

10. (Amended) The conjugate of claim [2] 62, wherein the glycoprotein has the sequence of human erythropoietin modified by the addition of from 1 to 6 glycosylation sites.

23. (Amended) The conjugate of claim [2] 62, wherein the glycoprotein has the sequence of human erythropoietin modified by the rearrangement of at least one glycosylation site.

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